

HETEROCYCLES, Vol.70, 2006, pp. 261 - 270. © The Japan Institute of Heterocyclic Chemistry
Received, 21st July, 2006, Accepted, 1st September, 2006, Published online, 5th September, 2006. COM-06-S(W)17

SELECTIVE 1,2- VS 1,4-ADDITION OF *N*-ARYLPHOSPHAZENES TO β,γ -UNSATURATED α -KETOESTERS. SYNTHESIS OF QUINOLINECARBOXYLATES[#]

Francisco Palacios*, Javier Vicario, Jesús M. de los Santos, and Domitila Aparicio

Department of Organic Chemistry I, Faculty of Pharmacy, University of The Basque Country, P.O. Box 450, 01080 Vitoria, Spain

Fax: (+34) 945 013049. e-mail: francisco.palacios@ehu.es

Abstract – Selective conjugate reaction (1,4-addition) of *N*-arylphosphazenes derived from triphenylphosphine to α,β -unsaturated carbonyl compounds yielded 2-quinolinecarboxylates. However, when more reactive phosphazene species derived from trimethylphosphine were used, selective reaction with the carbonyl carbon (1,2-addition) occurred and *N*-aryl-1-azadienes were obtained. Thermal 6π -azaelectrocyclization of these 1-azadienes afforded 4-quinolinecarboxylates.

INTRODUCTION

Quinoline ring systems have been a subject of interest during the last 120 years due to its wide occurrence in natural products, frequently showing biological activity.¹ Since the XVII century the quinoline derived alkaloid quinine (**I**) has been widely used to combat malaria and in the XX century quinine (**I**) was replaced by its stereoisomer quinidine (**II**), which nowadays has been substituted by the more efficient synthetic alkaloids chloroquine (**III**), quinacrine, or primaquine.

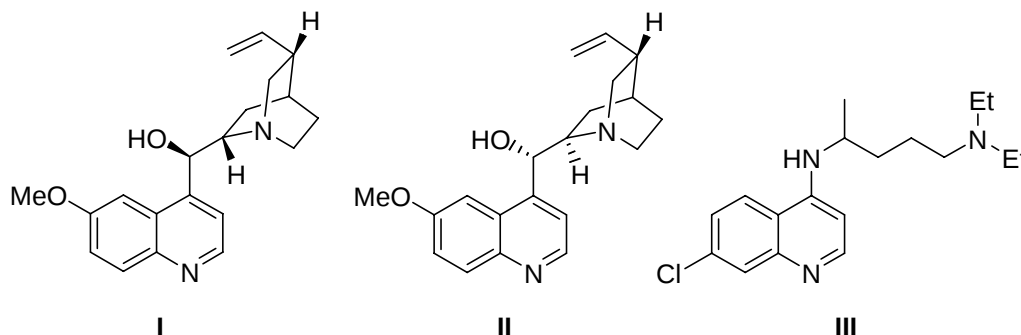
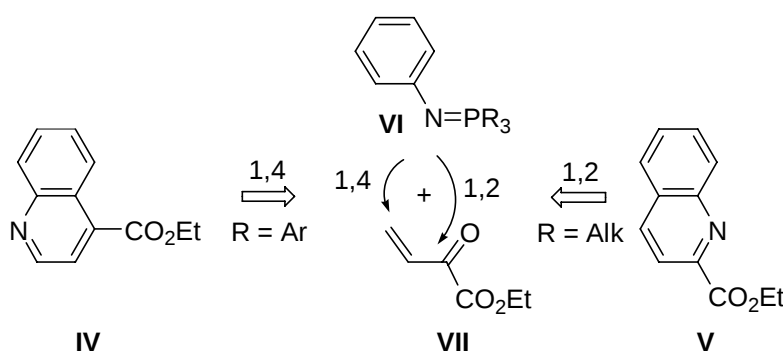


Figure 1. Quinoline derived antimalarial alkaloids.

[#] Dedicated to Prof. Steven M. Weinreb on the occasion of his 65th Birthday.

Moreover, besides the antimalarial² applications, a large variety of quinolines have displayed other potent pharmaceutical properties such as anti-inflammatory,^{3a} antiasthmatic,^{3b} antibacterial,^{3c} antihypertensive,^{3d} or for the treatment of tuberculosis^{3e} or Parkinson's disease^{3f} and a substantial number of molecules owning quinoline ring structures have been extensively used as general building blocks in organic synthesis.⁴ There are numerous methods for the preparation of quinolines. Most of the classical syntheses, developed in the latter XIX century, are based in reactions between amines and carbonyl compounds,⁵ but these methods only tolerate access to quinolines with low diversity in the substituents and more recently a huge branch of more versatile synthesis have been developed.⁶

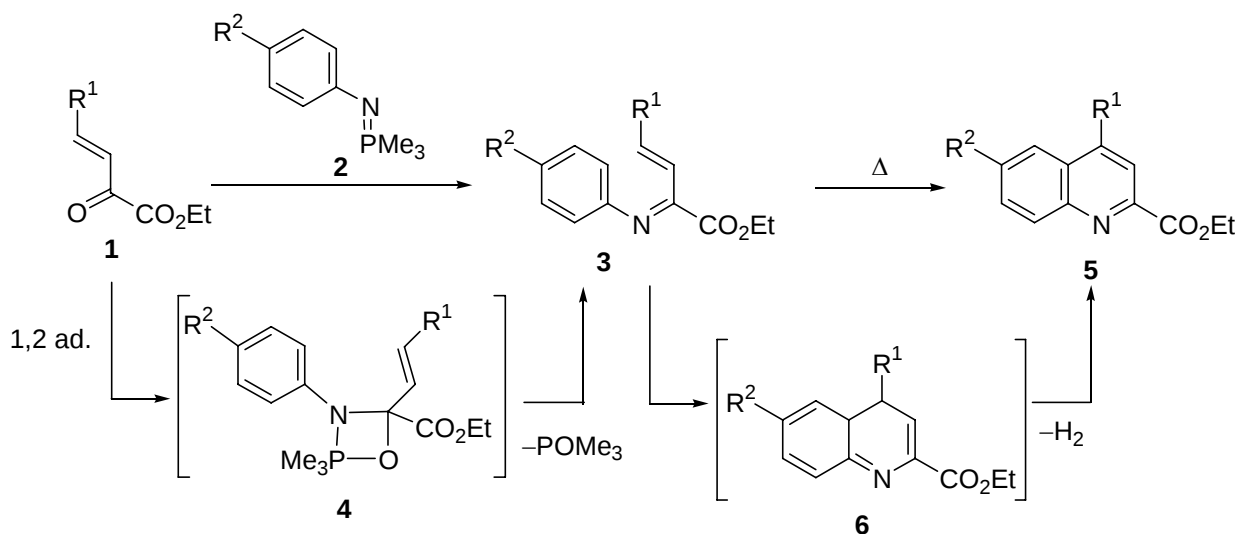
In this context, we have reported the synthesis 4-aminoquinolines⁷ from enamines and isocyanates as well as of phosphorylated quinolines⁸ from arylamines and functionalized carbonyl compounds and continuing with our interest in the synthesis and reactivity of six membered heterocycles and especially of quinolines, we report here the preparation of quinolinecarboxylates (**IV**) and (**V**), which are selectively generated either by 1,4- or 1,2-addition of *N*-aryl ($R = \text{Ar}$) or *N*-alkyl ($R = \text{Alk}$) phosphazenes (**VI**) to α,β -unsaturated carbonylic compounds (**VII**) (Scheme 1).



Scheme 1. Retrosynthesis of quinolines (**IV**) and (**V**).

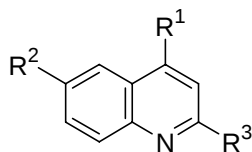
RESULTS AND DISCUSSION

Recently, we reported the synthesis of 1-azadienes derived from α -amino acids through aza-Wittig reaction of *N*-arylphosphazenes with β,γ -unsaturated α -ketoesters.⁹ The preparation of 1-azadienes derived from α -amino acids (**3**) is assumed to occur through nucleophilic 1,2-addition of *N*-aryl *P*-trimethylphosphazenes (**2**) to α,β -unsaturated carbonyl compounds (**1**), formation of a 4-membered oxazaphosphetane intermediates (**4**), and subsequent elimination of phosphine oxide in a typical aza-Wittig reaction mechanism¹⁰ (Scheme 2). These heterodienes (**3**) can be used for the preparation of functionalized quinolines. Thus, when *N*-aryl 1-azadienes (**3**) were heated, quinoline-carboxylates (**5**) were obtained in good yields (Scheme 2, Table 1, Entries 1-2 and 5-6).



Scheme 2. Synthesis of 2-quinolinecarboxylates from *N*-aryl-1-azadienes (**1**).

Table 1. Quinolines (**5**) and (**10**) synthesized.



Entry	Comp	R ¹	R ²	R ³	% Yield	
					1,2-ad ^a	1,4-ad ^b
1	5a	<i>p</i> -NO ₂ -C ₆ H ₄	Me	CO ₂ Et	83	-
2	5b	<i>p</i> -NO ₂ -C ₆ H ₄	MeO	CO ₂ Et	85	-
3	10a	CO ₂ Et	Me	<i>p</i> -NO ₂ -C ₆ H ₄	-	79
4	10b	CO ₂ Et	MeO	<i>p</i> -NO ₂ -C ₆ H ₄	-	79
5	5c(10c)	CO ₂ Et	Me	CO ₂ Et	80	83
6	5d(10d)	CO ₂ Et	MeO	CO ₂ Et	79	83

(a) From 1-azadienes (**3**); (b) From β,γ -unsaturated α -ketoesters (**1**).

Quinolines (**5**) were fully characterized by ¹H NMR, ¹³C NMR, EIMS and IR spectroscopy. Characteristic signals for quinoline (**5a**) in ¹H and ¹³C NMR spectra were assigned on the basis of COSY, DEPT and HETCOR experiments. ¹H NMR spectrum shows two doublets at δ = 8.31 and 7.70 ppm with a coupling constant ³J_{HH} = 8.6 Hz, corresponding respectively to the aromatic H-8 and H-7 of the quinoline ring and other two singlets at δ = 8.09 ppm for H-3 and δ = 7.54 ppm for H-5. ¹³C NMR spectrum shows four signals for the CH of the quinoline ring at δ = 132.7, 131.1, 123.5 and 121.1 ppm, corresponding to C-7, C-8, C-5 and C-3, respectively, as well as three signals for the three substituted quaternary carbons at δ = 146.9, 144.2, and 139.8 for C-2, C-4 and C-6, respectively. 2D NMR

experiments were carried out with quinoline (**5a**) in order to determine unambiguously the position of the substituents in the quinoline ring. For quinoline (**5a**) a correlation was observed between the aromatic CH of the *p*-NO₂-C₆H₄ substituent and the C-4 in the ring (Figure 2, *vide infra*). Formation of these quinolines (**5**) derived from α -amino esters can be explained through 6π -azaelectrocyclization¹¹ of azadienes (**3**) followed by spontaneous oxidation of the resulting dihydroquinoline intermediate (**6**) (Scheme 2, *vide supra*).

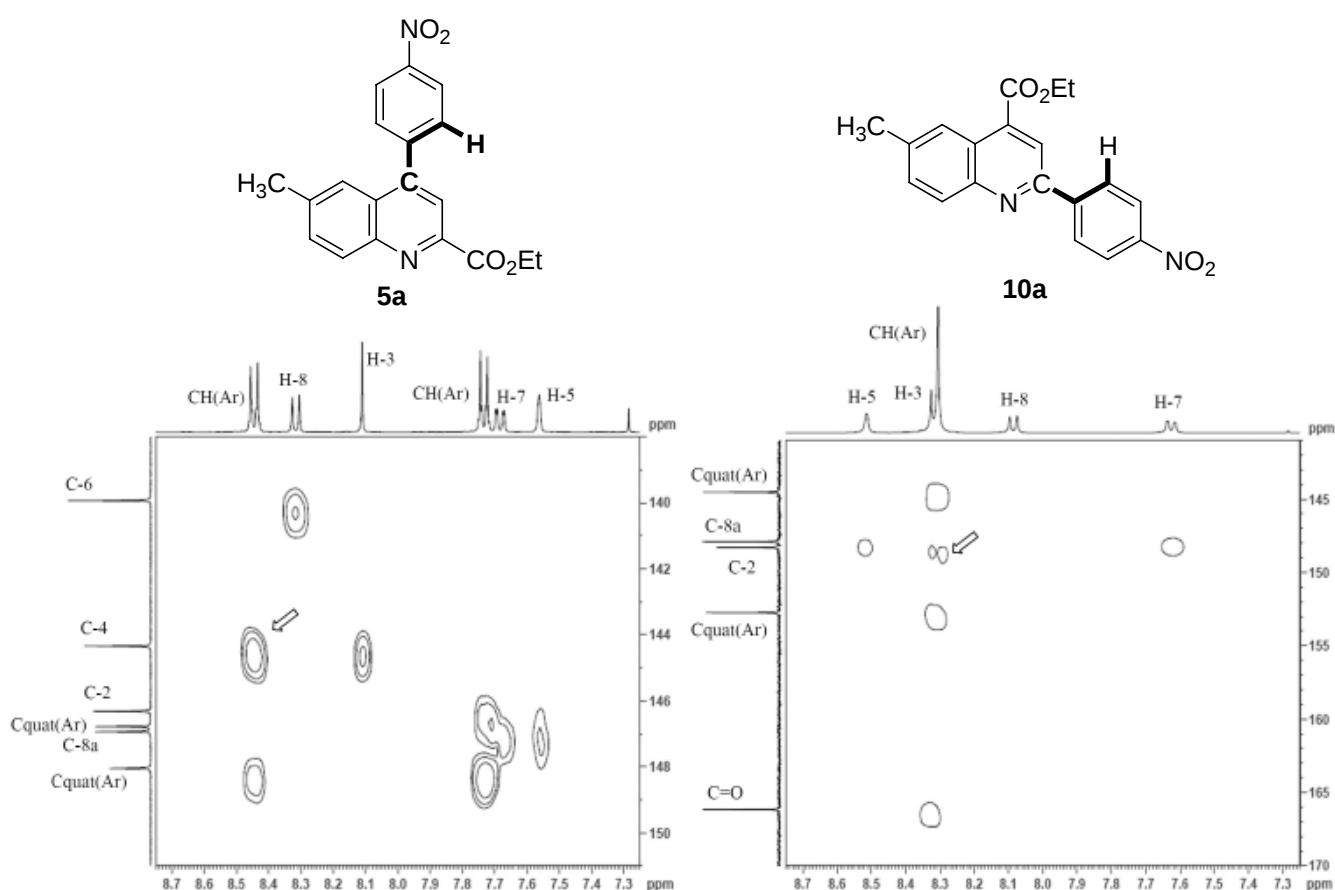
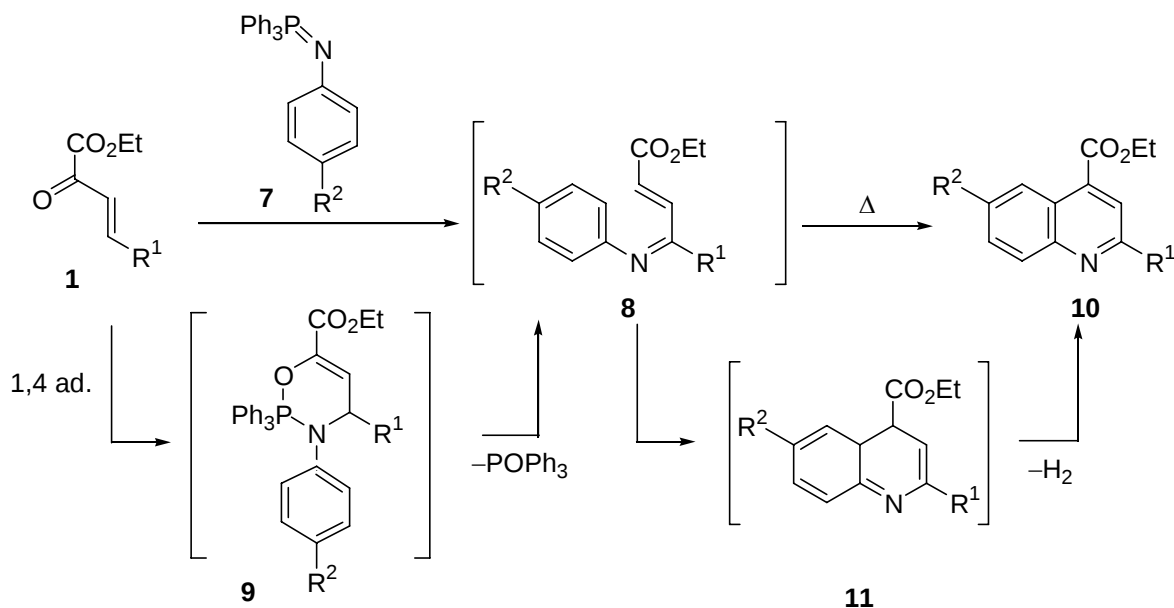


Figure 2. HMBC correlations for quinolines (**5a**) and (**10a**).

These results prompted us to explore, whether quinolines with the carboxylic group in position 4 could be also obtained from carbonyl derivative (**1**) and other phosphazenes, since the reactivity of phosphazenes as nucleophiles decreases when they are derived from trialkylphosphine, dialkylarylphosphine, alkyl diarylphosphine or triarylphosphine.¹⁰ Thus, no reaction of *N*-aryl *P*-triphenylphosphazene (**7**) with functionalized carbonyl compound (**1**) ($R^1 = p\text{-NO}_2\text{-C}_6\text{H}_4$) was observed at room temperature. However, when α -ketoesters (**1**) and *N*-aryl *P*-triphenylphosphazene (**7**) were heated in refluxing chloroform, quinolines (**10**) were obtained in good yields (Scheme 3, Table 1, Entries 3-6). Quinolines (**10**) were characterized by ¹H NMR, ¹³C NMR, EIMS and IR spectroscopy. 2D-NMR experiments were also carried out with quinoline (**10a**) and the correlation between the *p*-NO₂-C₆H₄ substituent and C-2 of the

quinoline ring was observed (Figure 2, *vide supra*), which is consistent with proposed structure for 4-quinolinecarboxylate (**10a**). The regioselective preparation of quinolines (**10**) could be explained by initial formation of the 6-membered oxazaphosphetane (**9**) through 1,4-addition of the phosphazene species (**7**) to the α,β -unsaturated carbonylic compound (**1**) and elimination of phosphine oxide to afford the non isolated 1-azadiene (**8**) and subsequent 6π -azaelectrocyclization with spontaneous oxidation of the dihydroquinoline intermediate (**11**) to yield quinolines (**10**).



Scheme 3. Synthesis of 4-quinoline-carboxylates from N -aryl phosphazenes (**7**) and ketoesters (**1**).

In conclusion, the results reported here involve an easy synthesis of substituted 2- and 4-quinolines. Thermal 6π -azaelectrocyclization of functionalized N -aryl 1-azadienes (**3**) gives 2-quinoline-carboxylates (**5**), while the addition of N -aryl P -triphenylphosphazenes (**7**) to α,β -unsaturated carbonyl compounds (**1**) affords 4-quinoline-carboxylates (**10**). 1,2- versus 1,4-addition of the phosphazene species to α,β -unsaturated ketones can be selectively performed by switching the methyl substituents by aryl substituents in the phosphazene group.

EXPERIMENTAL

General. Chemicals were purchased from Aldrich or Acros. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F₂₅₄ plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C (75 MHz) spectra were recorded on

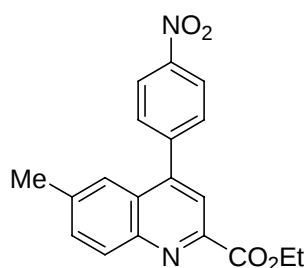
a Varian VXR 300 MHz spectrometer using CDCl_3 or CD_3OD solutions with TMS as an internal reference ($\delta = 0.00$ ppm). Mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 or 5973 spectrometer. Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr. Elemental analyses were performed in a LECO CHNS-932 apparatus. β,γ -unsaturated α -ketoesters (**1**)¹² and 1-azadienes (**3**)⁹ were synthesized according to literature procedures.

General procedure for the synthesis of quinolines (**5**) and (**10**).

Procedure A: a solution of 1-azadiene (**3**) (1 mmol) in xylene (3 mL) was stirred and refluxed until TLC indicated the disappearance of the starting material (24 to 48 h.). The resulting solution was concentrated under reduced pressure and the crude residue was purified by crystallization from Et_2O .

Procedure B: a solution of β,γ -unsaturated α -keto ester (**1**) (1 mmol) and the corresponding *N*-aryl phosphazene derived from triphenylphosphine (**7**) (1 mmol) in CHCl_3 (3 mL) was stirred and refluxed until TLC indicated the disappearance of the carbonylic compound (**1**) (24 to 48 h.). The solvent was then removed under reduced pressure and the crude residue was purified by chromatography (SiO_2 , AcOEt / hexanes 1:3).

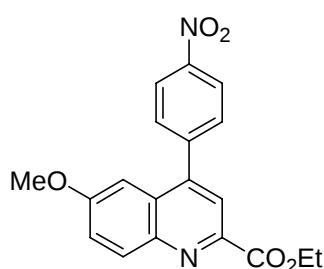
2-Ethoxycarbonyl-6-methyl-4-*p*-nitrophenylquinoline (5a**):** Synthesized according to the general



procedure A with ethyl 4-*p*-nitrophenyl-2-*p*-tolylimino-(*E*)-3-butenate (338 mg, 1 mmol), affording 303 mg (83 %) of **5a** as a yellow solid. mp 203–204 °C (Et_2O). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.43 (d, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, 2 CH_{ar}), 8.31 (d, $^3J_{\text{HH}} = 8.6$ Hz, 1 H, CH_{quin}), 8.09 (s, 1 H, CH_{quin}), 7.72 (d, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, 2 CH_{ar}), 7.70 (d, $^3J_{\text{HH}} = 8.6$ Hz, 1 H, CH_{quin}), 7.54 (s, 1 H, CH_{quin}), 4.58 (q, $^3J_{\text{HH}} = 7.0$ Hz, 2 H, CH_2O), 2.51 (s, 3 H, CH_3), 1.50 (t, $^3J_{\text{HH}} = 7.0$ Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 165.2 ($\text{C}=\text{O}$), 148.0 (C_{quat}), 146.9 (C_{quat}), 146.7 (C_{quat}), 146.2 (C_{quat}), 144.2 (C_{quat}), 139.8 (C_{quat}), 132.7 (CH), 131.1 (CH), 130.5 (2 CH), 126.9 (C_{quat}), 123.8 (2 CH), 123.5 (CH), 121.1 (CH), 62.3 (CH_2O), 22.0 (CH_3), 14.3 (CH_3). FTIR (KBr): ν_{max} (cm^{-1}): 1722 ($\text{C}=\text{O}$ st. ester). EIMS m/z (amu): 336 (M^+ , 3), 264 ($\text{M}^+ - \text{CO}_2\text{Et}$, 100). Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4$: C 67.85, H 4.79, N 8.33. Found: C 67.80, H 4.83, N 8.27.

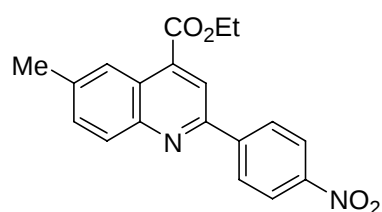
2-Ethoxycarbonyl-6-methoxy-4-*p*-nitrophenylquinoline (5b**):** Synthesized according to the general



procedure A with ethyl 2-*p*-methoxyphenylimino-4-*p*-nitrophenyl-(*E*)-3-butenate (354 mg, 1 mmol), affording 311 mg (85 %) of **5b** as a yellow solid. mp 203–204 °C (Et_2O). ^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.54 (d, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, 2 CH_{ar}), 8.53 (d, $^3J_{\text{HH}} = 8.5$ Hz, 1 H, CH_{quin}), 8.28 (s, 1 H, CH_{quin}), 7.74 (d, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, 2 CH_{ar}), 7.75 (d, $^3J_{\text{HH}} = 8.5$ Hz, 1 H, CH_{quin}), 7.32 (s, 1 H, CH_{quin}), 4.54 (q, $^3J_{\text{HH}} = 7.0$ Hz, 2 H, CH_2O), 3.91 (s, 3 H, CH_3).

CH₃O), 1.47 (t, $^3J_{\text{HH}} = 7.0$ Hz, 3 H, CH₃). ^{13}C NMR (75 MHz, CDCl₃) δ (ppm): 166.0 (C=O), 160.8 (C_{quat}), 148.1 (C_{quat}), 146.7 (C_{quat}), 146.5 (C_{quat}), 146.1 (C_{quat}), 144.0 (C_{quat}), 132.7 (CH), 131.2 (CH), 130.2 (2 CH), 126.5 (C_{quat}), 144.0 (2 CH), 123.4 (CH), 121.1 (CH), 62.2 (CH₂O), 56.0 (CH₃), 14.5 (CH₃). FTIR (KBr): ν_{max} (cm⁻¹): 1719 (C=O st. ester). EIMS m/z (amu): 352 (M^+ , 66), 279 ($\text{M}^+ - \text{CO}_2\text{Et}$, 100). Anal. Calcd for C₁₉H₁₆N₂O₅: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.80; H, 4.61; N, 7.98.

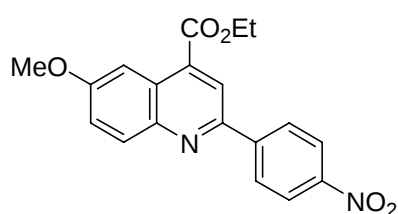
4-Ethoxycarbonyl-6-methyl-2-*p*-nitrophenylquinoline (10a): Synthesized according to the general



procedure B with ethyl 4-*p*-nitrophenyl-2-oxo-3-butenate (249 mg, 1 mmol) and *N*-(*p*-tolyl)-*P,P,P*-triphenylphosphine imide (440 mg, 1.2 mmol), affording 272 mg (79 %) of **10a** as a yellow solid. mp 163–164 °C (Et₂O). ^1H NMR (300 MHz, CDCl₃) δ (ppm): 8.50 (s, 1 H, CH_{quin}), 8.32–8.28 (m, 5 H, 2 CH_{ar} + CH_{quin}), 8.08 (d, $^3J_{\text{HH}} = 8.7$ Hz, 1 H, CH_{quin}),

7.61 (dd, $^3J_{\text{HH}} = 8.7$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, 1 H, CH_{quin}), 4.53 (q, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, CH₂O), 2.57 (s, 3 H, CH₃), 1.49 (t, $^3J_{\text{HH}} = 7.2$ Hz, 3 H, CH₃). ^{13}C NMR (75 MHz, CDCl₃) δ (ppm): 165.9 (C=O), 152.4 (C_{quat}), 148.1 (C_{quat}), 147.7 (C_{quat}), 144.2 (C_{quat}), 139.0 (C_{quat}), 135.5 (C_{quat}), 132.4 (CH), 130.0 (CH), 127.7 (2 CH), 124.3 (C_{quat}), 124.2 (CH), 123.7 (2 CH), 119.5 (CH), 61.9 (CH₂O), 22.1 (CH₃), 14.2 (CH₃). FTIR (KBr) ν_{max} (cm⁻¹): 1716 (C=O st. ester). EIMS m/z (amu): 336 (M^+ , 100), 263 ($\text{M}^+ - \text{CO}_2\text{Et}$, 55). Anal. Calcd for C₁₉H₁₆N₂O₄: C 67.85, H 4.79, N 8.33. Found: C 67.89, H 4.74, N 8.28.

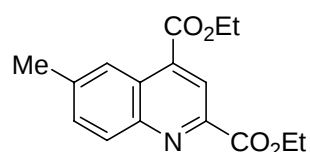
4-Ethoxycarbonyl-6-methoxy-2-*p*-nitrophenylquinoline (10b): Synthesized according to the general



procedure B with ethyl 4-*p*-nitrophenyl-2-oxo-3-butenate (249 mg, 1 mmol) and *N*-(*p*-methoxyphenyl)-*P,P,P*-triphenylphosphine imide (460 mg, 1.2 mmol), affording 281 mg (79 %) of **10b** as a yellow solid. mp 163–164 °C (Et₂O). ^1H NMR (300 MHz, CDCl₃) δ (ppm): 8.67 (s, 1 H, CH_{quin}), 8.35–8.23 (m, 5 H, 4 CH_{ar} + CH_{quin}), 8.00 (d, $^3J_{\text{HH}} = 8.7$ Hz, 1 H, CH_{quin}),

7.73 (dd, $^3J_{\text{HH}} = 8.7$ Hz, $^4J_{\text{HH}} = 1.7$ Hz, 1 H, CH_{quin}), 4.58 (q, $^3J_{\text{HH}} = 7.2$ Hz, 2 H, CH₂O), 3.96 (s, 3 H, CH₃O), 1.46 (t, $^3J_{\text{HH}} = 7.2$ Hz, 3 H, CH₃). ^{13}C NMR (75 MHz, CDCl₃) δ (ppm): 166.7 (C=O), 161.0 (C_{quat}), 152.2 (C_{quat}), 148.2 (C_{quat}), 147.5 (C_{quat}), 144.0 (C_{quat}), 135.5 (C_{quat}), 132.4 (CH), 129.8 (CH), 127.5 (2 CH), 124.4 (C_{quat}), 124.0 (CH), 123.7 (2 CH), 119.4 (CH), 61.8 (CH₂O), 54.9 (CH₃O), 14.2 (CH₃). FTIR (KBr) ν_{max} (cm⁻¹): 1716 (C=O st. ester). EIMS m/z (amu): 352 (M^+ , 100), 279 ($\text{M}^+ - \text{CO}_2\text{Et}$, 45). Anal. Calcd for C₁₉H₁₆N₂O₅: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.73; H, 4.54; N, 7.92.

2,4-Diethoxycarbonyl-6-methylquinoline (5c/10c): Synthesized according to the general procedure A

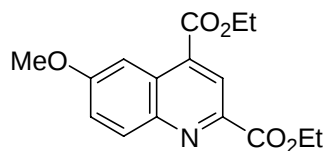


with ethyl 4-ethoxycarbonyl-4-*p*-tolylimino-(*E*)-2-butenate (289 mg, 1 mmol), affording 234 mg (80 %) of **5c/10c** as a white solid. Synthesized according to

the general procedure B with ethyl (*E*)-4-ethoxycarbonyl-4-oxo-2-butenate (200 mg, 1 mmol) and *N*-(*p*-tolyl)-*P,P,P*-triphenylphosphine imide (440 mg, 1.2 mmol), affording 243

mg (83 %) of **5c/10c** as a white solid. mp 109–110 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.57 (s, 1 H, CH_{quin}), 8.55 (d, ⁴J_{HH} = 1.8 Hz, 1 H, CH_{quin}), 8.19 (d, ³J_{HH} = 8.7 Hz, 1 H, CH_{quin}), 7.62 (dd, ³J_{HH} = 8.7 Hz, ⁴J_{HH} = 1.8 Hz, 1 H, CH_{quin}), 4.53 (q, ³J_{HH} = 7.0 Hz, 2 H, CH₂O), 4.49 (q, ³J_{HH} = 7.2 Hz, 2 H, CH₂O), 2.57 (s, 3 H, CH₃), 1.47 (t, ³J_{HH} = 7.0 Hz, 3 H, CH₃), 1.45 (t, ³J_{HH} = 7.2 Hz, 3 H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 165.9 (C=O), 165.0 (C=O), 147.4 (C_{quat}), 146.8 (C_{quat}), 140.8 (C_{quat}), 135.5 (C_{quat}), 132.7 (CH), 131.0 (CH), 126.3 (C_{quat}), 124.3 (CH), 122.1 (CH), 62.4 (CH₂O), 62.0 (CH₂O), 22.3 (CH₃), 14.3 (CH₃), 14.2 (CH₃). FTIR (KBr) ν_{max} (cm⁻¹): 1719 (C=O st. ester). EIMS m/z (amu): 287 (M⁺, 8), 214 (M⁺ – CO₂Et, 100). Anal. Calcd for C₁₆H₁₇NO₄: C 66.89, H 5.96, N 4.88. Found: C 66.95, H 5.91, N 4.91.

2,4-Diethoxycarbonyl-6-methoxyquinoline (5d/10d): Synthesized according to the general procedure A



with ethyl 4-ethoxycarbonyl-4-*p*-methoxyphenylimino-(*E*)-2-butenate (305 mg, 1 mmol), affording 245 mg (79 %) of **5d/10d** as a white solid. Synthesized according to the general procedure B with ethyl (*E*)-4-ethoxycarbonyl-4-oxo-2-butenate (200 mg, 1 mmol) and

N-(*p*-methoxyphenyl)-*P,P,P*-triphenylphosphine imide (460 mg, 1.2 mmol), affording 252 mg (83 %) of **5d/10d** as a white solid. mp 112–113 °C (Et₂O). ¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.67 (s, 1 H, CH_{quin}), 8.26 (d, ⁴J_{HH} = 2.7 Hz, 1 H, CH_{quin}), 8.22 (d, ³J_{HH} = 9.3 Hz, 1 H, CH_{quin}), 7.44 (dd, ³J_{HH} = 9.3 Hz, ⁴J_{HH} = 2.7 Hz, 1 H, CH_{quin}), 4.54 (q, ³J_{HH} = 7.0 Hz, 2 H, CH₂O), 4.49 (q, ³J_{HH} = 7.2 Hz, 2 H, CH₂O), 3.98 (s, 3 H, CH₃O), 1.48 (t, ³J_{HH} = 7.0 Hz, 3 H, CH₃), 1.47 (t, ³J_{HH} = 7.2 Hz, 3 H, CH₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 165.9 (C=O), 165.1 (C=O), 160.9 (C_{quat}), 145.2 (C_{quat}), 144.9 (C_{quat}), 133.7 (C_{quat}), 132.8 (CH), 128.3 (C_{quat}), 123.8 (CH), 123.0 (CH), 103.0 (CH), 62.3 (CH₂O), 61.9 (CH₂O), 55.7 (CH₃O), 14.4 (CH₃), 14.3 (CH₃). FTIR (KBr) ν_{max} (cm⁻¹): 1712 (C=O st. ester) EIMS m/z (amu): 303 (M⁺, 12), 230 (M⁺ – CO₂Et, 100). Anal. Calcd for C₁₆H₁₇NO₅: C 63.36, H 5.65, N 4.62. Found: C 63.30, H 5.68, N 4.58.

ACKNOWLEDGEMENTS

The present work has been supported by the Dirección General de Investigación del Ministerio de Ciencia y Tecnología (MCYT, Madrid DGI, PPQ2003-0910) and by the Universidad del País Vasco (UPV, GC 2002). J.V. thanks the Departamento de Educación, Universidades e Investigación del Gobierno Vasco, for a postdoctoral fellowship and J.M. de los Santos thanks the Ministerio de Ciencia y Tecnología (Madrid) for financial support through the Ramón y Cajal Program.

REFERENCES (AND NOTES)

1. For reviews see: J. P. Michael, *Nat. Prod. Rep.* 2005, **22**, 627 and references therein; J. P. Michael, 'Rodd's Chemistry of Carbon Compounds (2nd Edition)' Vol 4 (Part F), ed by M.

- Sainsbury, Elsevier: Amsterdam, 1998, pp. 423–482; Y. Morimoto, F. Matsuda, and H. Shirahama, *Synlett*, 1991, 202.
2. J. Wiesner, R. Ortmann, H. Jomaa, and M. Schlitzer, *Angew. Chem., Int. Ed.*, 2003, **43**, 5274; O. Bilker, V. Lindo, M. Panico, A. E. Etienne, T. Paxton, A. Dell, M. Rogers, R. E. Sinden, and H. R. Morris, *Nature*, 1998, **392**, 289; D. J. Sullivan, I. Y. Gluzman, D. G. Russell, and D. Goldberg, *Proc. Nat. Acad. Sci.*, 1996, **93**, 11865; C. M. Trenholme, R. L. Williams, R. E. Desjardins, H. Frischer, P.E. Carson, K. H. Rieckmann, and C. J. Canfield, *Science*, 1975, **190**, 792.
 3. P. G. Baraldi, M. A. Tabrizi, D. Preti, A. Bovero, F. Fruttarolo, R. Romagnoli, N. A. Zaid, A. R. Moorman, K. Varani, and P. A. Borea, *J. Med. Chem.*, 2005, **48**, 2001; R. D. Larsen, E. G. Corley, A. O. King, J. D. Carrol, P. Davis, T. R. Verhoeven, P. J. Reider, M. Labelle, J. Y. Gauthier, Y. B. Xiang, and R. Zamboni, *J. Org. Chem.*, 1996, **61**, 3398; A. K. Sadana, Y. Mirzab, K. R. Anejab, and O. Prakash, *Eur. J. Med. Chem.*, 2003, **38**, 533; N. Muruganantham, R. Sivakumar, N. Anbalagan, V. Gunasekaran, and J. T. Leonard, *Biol. & Pharm. Bull.*, 2004, **27**, 1683; K. Andries, P. Verhasselt, J. Guillemont, H. W. H. Göhlmann, J.-M. Neefs, H. Winkler, J. Van Gestel, P. Timmerman, M. Zhu, E. Lee, P. Williams, D. de Chaffoy, E. Huitric, S. Hoffner, E. Cambau, C. Truffot-Pernot, N. Lounis, and V. Jarlier, *Science*, 2005, **307**, 223; D. Liu, H. V. Wikström, D. Dijkstra, J. B. de Vries, and B. J. Venhuis, *J. Med. Chem.*, 2006, **49**, 1494.
 4. For reviews see: C. D. Johnson, In ‘Rodd’s Chemistry of Carbon Compounds (2nd Edition)’, ed. by M. Sainsbury, Elsevier: Amsterdam, 1998, 4 (Part F), pp. 129–161; D. L. Comins and S. O’Connor, *Prog. Het. Chem.*, 1997, **9**, 222; F. Palacios, D. Aparicio, G. Rubiales, A. M. Ochoa de Retana, and E. Martinez de Marigorta, In ‘Targets in Heterocyclic Systems’, ed. by O. A. Attanasi, D. Spinelli, Italian Society of Chemistry, Rome, 1997, pp. 187–223.
 5. Z. H. Skraup, *Monasch. Chem.*, 1880, **1**, 316; O. Doebner and W. von Miller, *Ber.*, 1881, **14**, 2812; P. Friedländer, *Ber.*, 1882, **15**, 2572; W. Pfitzinger, *J. Prakt. Chem.*, 1886, **33**, 100; M. Conrad and L. Limbach, *Ber.*, 1887, **20**, 944; A. Combes, *Bull. Soc. Chim. Fr.*, 1988, **49**, 89.
 6. For a review see: V. V. Kouznetsov, L. Y. Vargas Méndez, and C. M. Meléndez Gómez, *Curr. Org. Chem.*, 2005, **9**, 141. Some recent contributions to the synthesis of quinolines: K. O. Hessian and B. L. Flynn, *Org. Lett.*, 2006, **8**, 243; G.W. Wang, C.-S. Jia, and Y.-W. Dong, *Tetrahedron Lett.*, 2006, **47**, 1059; G. Chelucci, I. Manca, and G. A. Pinna, *Tetrahedron Lett.*, 2005, **46**, 767. M. G. Banwell, D. W. Lupton, X. Ma, J. Renner, and M. O. Sydnes, *Org. Lett.*, 2004, **6**, 2741; K. Motokura, T. Mizugaki, K. Ebitani, and K. Kaneda, *Tetrahedron Lett.*, 2004, **45**, 6029; T. Ishikawa, S. Manabe, T. Aikawa, T. Kudo, and S. Saito, *Org. Lett.*, 2004, **6**, 2361.
 7. F. Palacios, A. M. Ochoa de Retana, and J. M. Alonso *J. Org. Chem.*, 2005, **70**, 8895; F. Palacios, A. M Ochoa de Retana, J. I. Gil, and J. M. Alonso *Tetrahedron.*, 2004, **60**, 8937.

8. F. Palacios, D. Aparicio, Y. Lopez, and J. M. De los Santos, *Heterocycles*, 2006, **67**, 815; F. Palacios, A. M Ochoa de Retana, J. I. Gil, and J. M. Alonso *Tetrahedron: Asymmetry*, 2002, **13**, 2541.
9. F. Palacios, J. Vicario, and D. Aparicio, *J. Org. Chem.*, 2006, **71**, *In press*.
10. F. P. Cossio, C. Alonso, B. Lecea, M. Ayerbe, G. Rubiales, and F. Palacios, *J. Org. Chem.*, 2006, **71**, 2839; F. Palacios, E. Herran, and G. Rubiales, *J. Org. Chem.*, 1999, **64**, 6239.
11. E. N. Marvell. "Thermal Electrocyclic Reactions", Academic Press, New York, 1980.
12. F. Palacios, J. Vicario, and D. Aparicio, *Eur. J. Org. Chem.*, 2006, 2843.